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Iodination of Phenol

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**Risø National Laboratory, DK-4000 Roskilde, Denmark
January 1990**

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IODINATION OF PHENOL

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ABSTRACT

Phenol is iodinated in aqueous solution at pH 5 (acetate buffer) by elemental iodine or, if the iodine is present as iodide, enzymatically controlled by peroxidases. Generally mono-, di- and triiodophenols are obtained, the overall product composition being virtually identical for the two iodination modes. However, there is a tendency to a higher *para* to *ortho* ratio for the enzymatically controlled reaction. The mutual ratios of the single iodophenols depends on the initial concentration ratio between phenol and the iodinating species. The first step in the iodination leads preferentially to substitution in the *ortho* position rather than in the *para* position in contrast to *e.g.* the corresponding bromination. The relative rates of the competitive reactions in the combined iodination scheme has been derived.

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1. INTRODUCTION

For many years major attention to the environmental cycle of iodine has been paid due to its status as essential element to man. In recent years, after the introduction of nuclear power as an energy source, the environmental cycle of iodine has received renewed interest due to the possible release of the longlived radioactive ^{129}I isotope, *e.g.* during reprocessing.¹ Man concentrates iodine in the thyroid gland. Hence, high ^{129}I levels in the environment, and subsequently high levels in the human thyroid gland may cause severe damages, *i.e.* development of cancer.

It is generally believed that iodination of tyrosin in the thyroid gland is a reaction, which is catalyzed by an enzyme of the peroxidase group, "thyroid peroxidase", in the presence of hydrogen peroxide.² Thus, it seems resonable to assume that enzymes of the peroxidase group are able to catalyze the iodination of phenols by iodide in the presence of hydrogen peroxide.

As a preliminary study to investigations on the possible enzymatically mediated iodination of naturally occurring phenolic compounds, as humic substances, in the terrestrial environment, we report in the present paper on the iodination of phenol by elemental iodine and by iodide in the presence of hydrogen peroxide applied lactoperoxidase (LP) as the enzyme catalyst.

2. EXPERIMENTAL

2.1. Chemicals

Phenol (*p.a.*) and 2-iodophenol (*p.a.*) were obtained from Merck. 4-iodophenol (99%) and 2,4,6-triiodophenol were obtained from Aldrich-Chemie. NaI (Merck *p.a.*), ^{131}I as NaI, Lactoperoxidase (EC.1.11.1.7.) (Sigma L-2005), Acetate buffer pH 5, NaHSO_3 (J.T. Baker Chemicals) and HCl (FERAC zur analyse).

2.2. Preparation of iodophenols by direct iodination (by I₂) of phenol

A solution of 9,4 g (0,1 mole) phenol and 28 g (0,11 mole) I₂ in 1000 mL acetatebuffer (pH 5) were stirred for 50 h. Remaining iodine was reduced with 55 mL 0.4 M Na₂S₂O₃. The solution was extracted with 4 x 125 mL diethyl ether. The combined organic layers were washed with 4 x 100 mL 0,1 M NaHCO₃, dried (Na₂SO₄) and evaporated to an oily substance under reduced pressure. The diiodophenols were separated by means of preparative HPLC applying a 250x16 mm Lichrosorb RP18 (5 µm) column (Eluent: MeOH/H₂O 70/30 v/v (33 min) and subsequent pure MeOH (3 min), Flow rate: 5 mL/min, UV-detec.: 280 nm).

2.3. Variation of the initial phenol concentration

In a total volume of 10 mL acetatebuffer pH 5 , phenol, NaI, H₂O₂ and lactoperoxidase were allowed to react, the NaI being spiked with ¹³¹I. Initial concentrations of NaI and H₂O₂ were 10⁻⁴ M and 10 µg lactoperoxidase (E.C. 1.11.1.7.) corresponding to approximately 0.8 units were used. The phenol concentration was varied in the range from 3.3 x 10⁻⁵ to 2 x 10⁻⁴ M. After mixing phenol, NaI and H₂O₂ the reactions were initiated by addition of the enzyme and were allowed to proceed for 10 min. at ambient temperature. The solutions were analyzed by means of HPLC without further treatment applying a 250x4.6 mm Nucleosil C8 (10 µm) column (Eluent: MeOH/H₂O 50/50 v/v, Flow rate: 1 mL/min). Control experiments without applying lactoperoxidase were carried out analogously.

2.4. Enzymatic iodination of ¹⁴C-phenol

In a total volume of 10 ml acetatebuffer pH 5 phenol at a conc. 3.3 x 10⁻⁵ (spiked with ¹⁴C-phenol) was enzymatically iodinated as described above (cf. 2.3.).

2.5. Experiments investigating the rates of the respective iodination reactions

Phenol and iodophenols were iodinated as single species as well as in combination, the procedure being as outlined above, however, applying phenol and/or iodophenols in ten-fold excess compared to iodide. The following system were studied: a) phenol, b) phenol + 2-iodophenol, c) phenol + 4-iodophenol, d) 2-iodophenol, e) 4-iodophenol, f) phenol + 2,6-diiodophenol, g) phenol + 2,4-diiodophenol, h) 2,6-diiodophenol and i) 2,4-diiodophenol. The concentrations of the phenols were 1×10^{-4} M whereas iodide and hydrogen peroxide concentrations were kept at 1×10^{-5} M. Lactoperoxidase concentrations were 10 μ g/10 ml. The reaction mixture were analyzed by means of HPLC (*vide supra*).

2.6. Comparison of iodination and bromination of phenol applying elemental iodine and bromine, respectively

In a total volume of 50 mL (acetate buffer, pH 5) phenol (10^{-2} M) is reacted with the appropriate elemental halogen (10^{-3} M). Excess of phenol is used in order to avoid consecutive halogenation of the primary formed monohalogenated phenols. After complete decolorization of the reaction mixture pH was adjusted to 1 (HCl). The reaction mixture was extracted with diethyl ether (2x100 mL). The combined organic layers were dried (sodium sulphate) and evaporated to dryness. The product was dissolved in 1 mL pyridine and hexamethyl disilazane (250 μ L) and trimethyl chlorosilane (250 μ L) were added.³ The mixture was centrifugated and the supernatant subjected directly to gas chromatographic analysis, applying a 30 m x 0.52 mm capillary DB-1 column (150°C isotherm./FID).

2.7. Iodination of phenol by iodide and chloramine-T

To 1 mL H₂O containing 0.220 g chloramine-T was added 1 mL H₂O containing 0.118 g NaI (spiked with ¹³¹I). After 2 min 1 mL H₂O containing

0.062 g phenol was added to the mixture. After 1 h 10 mL of 50% MeOH was added, and the reaction mixture was analyzed directly by means of HPLC.

The experiment was repeated without ^{131}I . The 3 mL of reaction mixture was added to 10 mL H_2O , and extracted with 25 mL ethylacetate. The organic layer was dried (Na_2SO_4) and evaporated to a volume about 2 mL. The product was analyzed by means of MS.

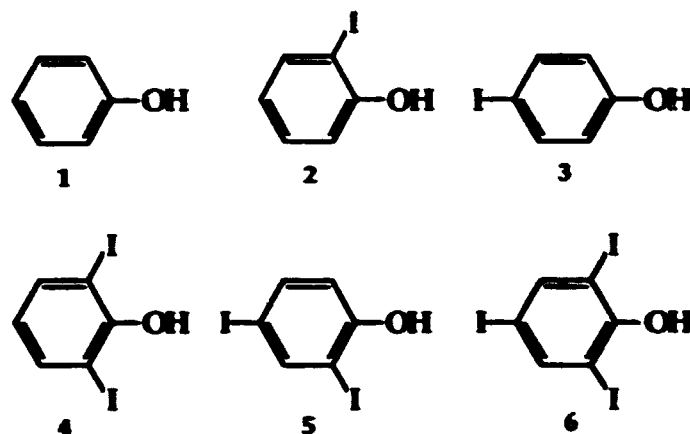
2.8. Reaction of mono-iodophenols with chloramine-T

Chloramine-T (7 mg) was added to 25 mL of 10^{-3} M aqueous solutions of 2-iodophenol or 4-iodophenol, respectively. The mixtures were stirred for 1 h, extracted with 25 mL ethylacetate. The organic layer was dried (Na_2SO_4) and evaporated to a volume about 2 mL. The products were analyzed by means of MS.

3. RESULTS AND DISCUSSION

3.1. Iodination by aqueous iodine and by iodide mediated by lactoperoxidase

The direct iodination of phenol (1) by aqueous I_2 turned, not unexpected out to give five different iodophenols: 2-iodophenol (2), 4-iodophenol (3), 2,6-diiodophenol (4), 2,4-diiodophenol (5) and 2,4,6-triiodophenol (6). The single compounds were indentified by comparison with authentic compounds. The product distribution was in accordance with the combined electronic effect of the OH-group (activating positions 2 and 4) and iodine (deactivating positions 2 and 4). When phenol is iodinated in dilute solutions (10^{-4} M) of aqueous iodine, nearly all the iodine was consumed within few minutes forming iodophenols.



Iodide does not react with phenol in the absence of an oxidizing agent.

Operating in relatively high concentrations of iodide and hydrogen peroxide, elemental iodine is formed in concentrations sufficiently high to interact with the phenol, possibly *via* a primary formation of hypiodous acid (HOI) as the actual iodinating species (*vide infra*). However, for I^- and H_2O_2 concentrations below ca. 10^{-4} M apparently no iodophenols could be detected within 10 min. Hence, the enzyme catalysis may play a crucial role in the possible iodination of phenol in the low concentration ranges as *e.g.* expected in the environment. It is in this context worthwhile to note that the enzymatically catalyzed iodination *a priori* will lead to 100% consumption of the iodide in the reaction mixture, whereas, in the possible absence of an oxidizing agent, only a 50% consumption, as a maximum, can be expected using elemental iodine/hypiodous acid as iodinating species, leaving the remaining 50% as iodide.

HPLC analysis of the products from the enzymatically mediated iodination of phenol showed no discrepancies compared to that originating from the direct iodination. Enzymatic iodination of phenol using ^{131}I and ^{14}C -phenol, respectively, showed ^{131}I and ^{14}C labeling at the same five positions in the HPLC trace, strongly indicating that the same 5 iodophenols were produced (fig. 1 & 2).

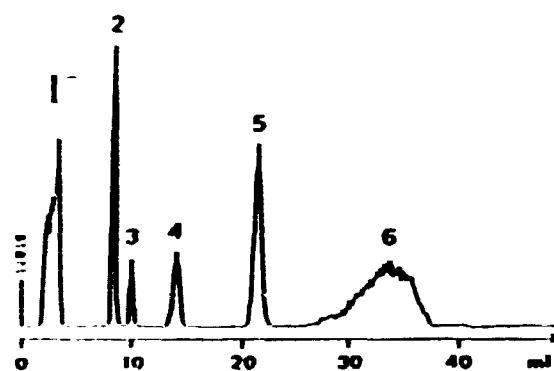


Fig. 1. HPLC trace of the product from enzymatic iodination of phenol using ^{131}I , detecting the radioactivity signal.

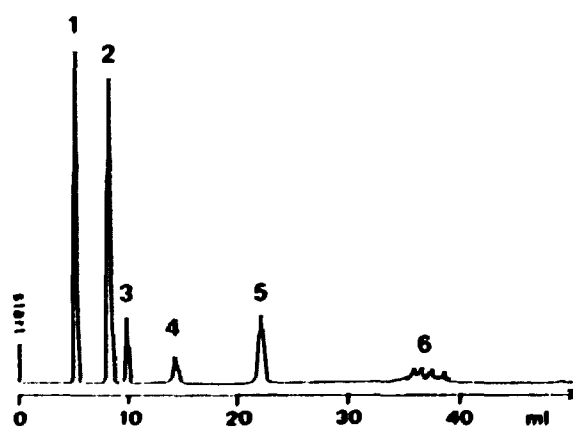


Fig. 2. HPLC trace of the product from enzymatic iodination of phenol using ^{14}C phenol, detecting the radioactivity signal.

For fixed initial I^- concentrations equal to 10^{-4} M and varying phenol concentrations (3.3×10^{-5} , 5.0×10^{-5} , 1.0×10^{-4} and 2.0×10^{-4} M), the relative yields of the single iodophenols are elucidated by HPLC analysis as visualized in fig. 3.

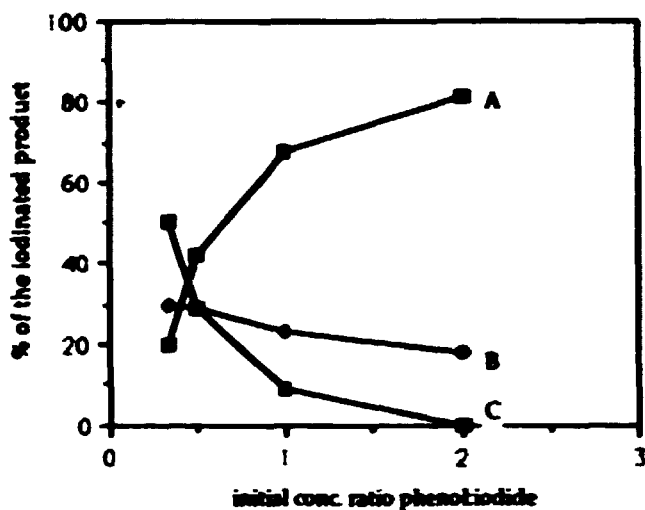
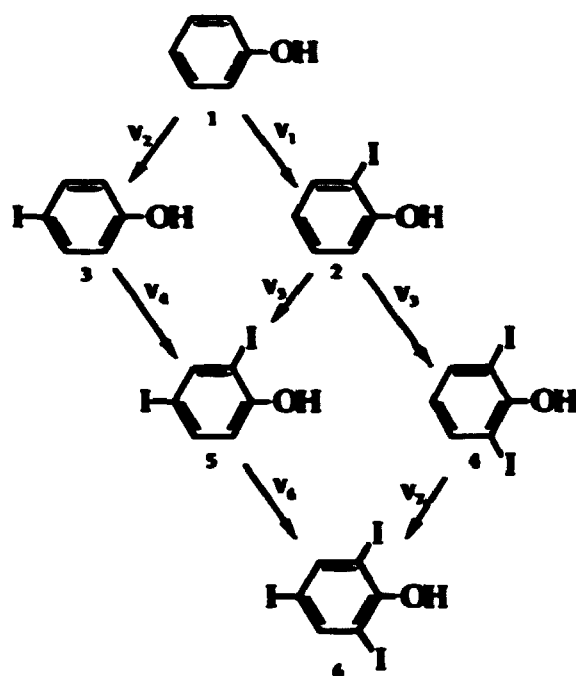


Fig. 3 The percentage of A: mono-, B: di-, and C: triiodophenols among the products originating from enzymatic iodination of phenol as a function of the initial phenol:iodide concentration ratio.

It is immediately seen (fig.3) that moniodophenol, not surprisingly, dominates when the initial phenol/ I^- concentration ratio is relatively high and that the degree of di- and tri-iodination increases with decreasing initial phenol/ I^- ratio. Thus, since the enzymatic iodination does not give rise to other isomers than does the direct iodination, *i.e.* by elemental iodine, of phenol, the iodination reaction obviously can be formulated as series of consecutive steps from phenol to mono-, di-, and tri-iodophenol, controlled by concentrations of reactants as well as the mutual rate constants.



Scheme 1

In order to elucidate the relative rates of the "competitive" iodination reactions different combinations of phenol and iodophenols were iodinated enzymatically, the phenols being applied in large excess. Thus, only the first iodo-derivatives from the parent molecules are formed. Taking into account that iodination of phenol may lead to 2- and 4-iodophenol, the probability of producing the former being twice that of the latter, it could be concluded that 2-iodophenol is produced with a rate approximately three times faster than 4-iodophenol. The relative reaction rates, based on product distributions, are given in Table 1.

Table 1. Relative rate relations of iodination based on product distribution.

Reactants	rate relation
Phenol,	$V_1 > V_2$
2-iodophenol	$V_3 > V_5$
Phenol, 2-iodophenol	$V_3 \geq V_1 + V_2$
	$V_5 \sim V_1 + V_2$
Phenol, 4-iodophenol	$V_4 \sim V_2$
Phenol, 2,4-diiodopheno'	$V_7 \gg V_1$
Phenol, 2,6-diiodophenol	$V_6 \ll V_1$

Iodination of 2-iodophenol lead to 2,6- and 2,4-diiodophenol in the ratio approx. 1,7 : 1. Iodinating mono-iodophenols in combination with phenol and calculating the rates relative to the iodination rate of phenol, lead to the conclusion that the 6-position in 2-iodophenol was about equal as favourable as the original 2-position in phenol. On the other hand, the 2- and 6-position in 4-iodophenol surprisingly appeared significantly less favorable for iodination. However since we operate in relatively high concentrations of the phenols (10^{-4}), it cannot be excluded that the relative rates determined under these conditions are influenced by an interaction between iodophenols and the enzyme reflecting an inhibiting tendency. Enzymatic iodination of 2,6-diiodophenol and 2,4-diiodophenol caused formation of 2,4,6- triiodophenol. However, when phenol is available as substrate, 2,4-diiodophenol will only to a very minor degree, if at all, be iodinated. In contrast the rate of forming 2,4,6-triiodophenol from 2,6-diiodophenol

appeared significantly higher than that of forming monoiodophenol from phenol.

From the relative reaction rates it can be concluded that in general the activation of the carbon-atoms for further iodination increases with degree of iodination. Activation of the actual C-atoms appears to be: phenol < mono-iodophenol < diiodophenol, except in the case when the 4-position is occupied by iodine. An explanation may be a possible interaction between the enzyme and the iodine atom located in 4-position, since the 4-position in 2,6-diiodophenol is very favourable for further iodination. However, an enzymatically controlled iodine exchange of iodine in the 4-position may also cause the observed effect.

When 2,4-diiodophenol is enzymatically iodinated applying ^{131}I labelling, ^{131}I labelled 2,4-diiodophenol is formed. The exchange reaction does not proceed in the absence of enzyme. Further more, it was observed that 2,6-diiodophenol shows no exchange reaction. Upon iodination of 4-iodophenol applying ^{131}I minor amounts of ^{131}I labelled 4-iodophenol was noted. Hence, it appears obvious to conclude that only the iodine in the 4-position is subject to enzymatically controlled iodine exchange, possibly *via* a simple electrophilic iodine-iodine substitution.

Upon increase of the initial ratio of phenol/ I^- the amount of triiodophenol formed as well as the ratio between the amounts of 2,4- and 2,6-diiodophenol decreases. This is in agreement with the above due to the fact that 2,4,6-triiodophenol was formed from 2,6-diiodophenol but not from 2,4-diiodophenol when alternative substrates, e.g. phenol were available. Since 2,6-diiodophenol only gave rise to 2,4,6-triiodophenol, the ratio 2,4-diiodophenol/2,6-diiodophenol increase, when the triiodophenol content increases.

Also of interest is that enzymatically controlled iodination of phenol in excess of hydrogen peroxide (compared to the conc. of iodide) causes the

formation of 2-iodophenol dimers, whereas 4-iodophenol apparently is not a subject to dimerization. The 2-iodophenols are probably linked through the other *ortho*-carbons. Danner et al.⁴ demonstrated the enzymatically catalyzed dimerisation of phenol through the *ortho*-carbons.

It is interesting to note that the production of 2-iodophenol apparently is strongly favoured relative to 4-iodophenol. For the enzymatically controlled iodination we found a 2:3 ratio equal to ca. 6:1, corresponding to a 86% yield of 2. The direct iodination, using elemental iodine afforded an even higher 2:3 ratio, as 92% of 2 was found. However, bromination of phenol on applying elemental bromine leads to the formation of only 23% of 2-bromophenol, in agreement with recent results reported by Tee et al.,⁵ who found a preference for para substitution at pH 4. In Table 2 some *ortho/para* ratios for halogenation of phenol in aqueous solutions are listed.

Table 2. *Ortho/para* ratios of the products formed, halogenating phenol

Reaction	pH	<i>ortho/para</i>	
Phenol, Bromine	pH 5	0.30	} This work
Phenol, Iodine	pH 5	13.3	
Phenol, NaOCl	pH 4	0.64	} (Ogata et al. 1989)
Phenol, NaOCl	pH 7	1.8	
Phenol, NaOCl	pH 8.8	2.8	
Phenol, NaOCl	pH 10	4.3	

From Table 2 it can be seen that at pH 5 the *ortho*-position is strongly favoured for iodination, while in the case of bromination apparently the para-position is favoured. At alkaline pH, Tee et al.⁵ suggested that the

ortho/para ratio changed towards increasing values when brominating phenol. However, they applied equal amounts of phenol and bromine. Thus, poly-brominated phenols were formed. This may distort the *ortho/para* ratio by possible preferential consumption of *ortho*-bromophenol.⁵

Based on theoretical considerations, Ogata et al.⁶ suggested that the *para*-position both in phenol and in the phenoxide ion as well as in anisole should be favoured for electrophilic substitution relative to the *ortho*-position. In their study of phenol chlorination, however, they concluded that some of the calculations support a mechanism, involving the formation of PhOCl, which subsequently may rearrange into *ortho*-chlorophenol. The mechanism is further supported by the increase of the *ortho/para* ratio, which increases with increasing pH (Table 2) and that chlorination of anisole leads to the expected *ortho/para* ratio based on the theoretical calculations Ogata et al.⁶ An analogous mechanism may be involved in the iodination of phenol.

3.2. Iodination by iodide mediated by chloramine-T

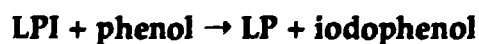
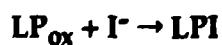
Chloramine-T mediated iodination of phenol in acetatebuffer (pH 5) leads to an *ortho/para* ratio between 0.5 and 1. However, the iodide/phenol ratio was 1 and the formation of a considerable amount of di-iodophenol was observed. It can be noted that only 2,4-diiodophenol and not 2,6-diiodophenol was observed, which strongly suggests that the di-iodophenol was formed from 4-iodophenol. Kometani et al.⁷ found 96% formation of 4-iodophenol by chloramine-T mediated iodination of phenol in dimethylformamide and dimethylsulfoxide. In this context it is important to note that attempts to iodinate phenol with elemental iodine in dimethylformamide revealed an extremely slow reaction, as less than 10% of the introduced iodine had reacted within 24 h. However, the predominance of 4-iodophenol was unambiguous. These findings suggest that chloramine-T mediated iodination involves a mechanism other than

iodination by elemental iodine. It should be noted that in dimethyl formamide the iodine-iodine bond in elemental iodine is strongly polarized, however, the reaction leading to the effective iodinating species, hypiodous acid, as in aqueous solution, obviously is absent.

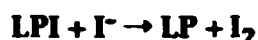
When treating 2-iodophenol and 4-iodophenol, respectively, with chloramine-T in acetatebuffer (pH 5), 2-iodophenol is not detectable by means of MS after one hour, but 4-iodophenol seems to be unaffected. These findings may distort the results because selective transformation of 2-iodophenol to some unknown compounds will obviously decrease the *ortho/para* ratio. It can also be noted that chloramine-T mediated iodination of phenol in acetatebuffer leads to the formation of unknown iodine-containing compounds. These species, which were difficult to elute from the HPLC column, may possibly consist of iodinated polymeric species involving the chloramine-T.⁸ By means of MS no dimers of iodophenol were found, contrary to the enzymatically controlled iodination of phenol in excess of hydrogen peroxide where dimers of 2-iodophenol were produced.

3.3. Mechanistic considerations

According to Morrison and Schonbaum⁹ the peroxidase may be oxidized by H₂O₂. They suggest that the oxidized form of the enzyme will interact with I⁻ leading to an enzyme-iodine complex, which apparently is the electropositive iodine species, which by electrophilic attack on one of the negatively charged sites in phenol leads to the iodinated species leaving the reduced lactoperoxidase:



It is well known that lactoperoxidase in the presence of iodide and hydrogen peroxide may lead to the formation of elemental iodine.¹⁰ Thus, we have to consider an alternative reaction, in which a primary formation of elemental iodine appears crucial.



It is well established that elemental iodine in aqueous solution exists in an equilibrium with hypiodous acid (HOI). Even at pH 5 significant amount of HOI apparently is present.¹¹ Thus, Niedleman and Geigert¹² suggest that the iodinating species is HOI. They concluded that the results of peroxidase mediated iodination can be explained by the operation of hypiodous acid. To elucidate the possible involvement of HOI we compared the iodination of phenol (acetate buffer, pH 5) with aqueous elemental iodine and hypiodous acid, respectively.

When phenol (3.3×10^{-3} mole/L) was iodinated at pH 5 by aqueous elemental iodine (3.3×10^{-4} mole/L), only 6 - 7 % of the mono-iodophenol formed was 4-iodophenol whereas 93-94% 2-iodophenol was detected. When elemental iodine was treated with equivalent amounts of NaOH the solution turned colourless, due to the formation of HOI. After adjusting pH to 5 by acetate buffer (the solution was still colourless), phenol was added. The product constituted of 2-iodophenol and 4-iodophenol in the same ratio as above. This strongly indicates that the same iodinating species, probably HOI, operates in both cases.



Especially it should be noted that the operation of hypiodous acid apparently explains the surprisingly high *ortho/para* ratio observed, although it is not obvious if the formation of *ortho*-iodophenol involves an intermediary

hypoiodite structure Ph-OI, which rearranges into the iodo-phenol, or if the HOI, by hydrogen bonding structurally is located in a position favourable for *ortho*-substitution. It is in this context once more worthwhile to mention the apparent predominance for *para*-substitution of phenol by interaction with elemental iodine in dimethylformamide.

In the present study we have not been able unambiguously to elucidate if the enzymatically controlled iodination of phenol takes place by interaction of phenol and the enzyme-iodine complex or by a reaction with primary formed elemental iodine/hypoiodous acid. However, it seems most reasonable to assume that both mechanisms are operating. The pronounced predominance for *ortho*-substitution found, also in the case of the enzymatically controlled reaction, strongly suggests the engagement of elemental iodine/hypoiodous acid in the iodination reaction, as it appears less likely that an interaction between the OH-moiety in the phenol and the enzyme-iodine complex should lead to the high 2:3 ratio observed. On the other hand, the tendency towards a decreased 2:3 ratio in the enzymatically controlled iodination relative to that observed for the direct iodination applying elemental iodine suggests at least some participation of a reaction between phenol and the enzyme-iodine complex. In an attempt to rationalize the above findings, we suggest that as long as iodide is present in the reaction mixture in reasonably high concentrations the latter will act as substrate for the enzyme-iodine complex leading to the formation of elemental iodine, and, hence, hypoiodous acid, which consecutively reacts with phenol. However, upon decreasing the iodide concentration during the reaction, phenol constitutes as an alternative substrate for the enzyme-iodine complex, a reaction which apparently leads to an enhanced *para*-substitution. Thus, iodination of phenol (10^{-4} M) applying iodide concentrations equal to 10^{-5} , 2.5×10^{-6} , and 10^{-6} M, respectively, lead to formation of 14.4, 18.4 and 20.6% 4-iodophenol, respectively.

4. CONCLUDING REMARKS

In 1984 Whitehead¹³ stated that the typical iodine content in soils is 0.5 - 20 mg/kg corresponding to 4×10^{-6} to 1.6×10^{-4} M/kg. Obviously the here applied iodide concentrations at 1×10^{-5} to 1×10^{-4} M agree well with those found in the environment. It can be mentioned that concentrations in rain, as source for soil water are about three orders of magnitude lower.¹³ As no iodophenols in detectable amounts in the present study were formed in the absence of enzyme, and since we observed that close to 90% of iodide is consumed when enzyme was available, it seems obvious that even small amounts of enzyme will increase the reaction rate dramatically. The present study has demonstrated that phenol even in rather low concentrations easily can be iodinated by I^- in the presence of lactoperoxidase and of H_2O_2 and that both mono-, di-, and tri-iodinated derivatives are formed.

Taking into account that extracellular peroxidases as well as H_2O_2 are available in most soils and humic acids contain approximately 20% phenolic, moieties¹⁴ the results in the present work do support the hypothesis of enzymatically controlled iodination of humic substances in soil and further investigations on other model molecules as well as on humic acids of different origin are in progress.

Finally, it should be mentioned that in the case of enzymatically controlled iodination of phenol the hydrogen peroxide/iodide ratio appears to play a crucial role in determining the eventual yields of 2-iodo- and 4-iodophenol, respectively. Thus, whenever the hydrogen peroxide concentration exceeds that of the iodide ions other peroxidation reactions may operate. In the present case it was demonstrated that an excess of hydrogen peroxide relative to iodide lead to a consecutive peroxidase controlled reaction yielding significant amounts of a 2-iodophenol dimer in agreement with previous results demonstrating peroxidase induced polymerizations of phenols.^{4,15} It is in this context interesting to note that 4-iodophenol apparently is not

affected by lactoperoxidase/hydrogen peroxide.

Obviously, the halogenation of phenol is not as simple as could be expected. Further elucidation of the interaction of different halogenating species with phenol is necessary if the mechanisms involved are to be described in detail.

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<p>Phenol is iodinated in aqueous solution at pH 5 (acetate buffer) by elemental iodine or, if the iodine is present as iodide, enzymatically controlled by peroxidases. Generally mono-, di- and triiodophenols are obtained, the overall product composition being virtually identical for the two iodination modes. However, there is a tendency to a higher <i>para</i> to <i>ortho</i> ratio for the enzymatically controlled reaction. The mutual ratios of the single iodophenols depends on the initial concentration ratio between phenol and the iodinating species. The first step in the iodination leads preferentially to substitution in the <i>ortho</i> position rather than in the <i>para</i> position in contrast to <i>e.g.</i> the corresponding bromination. The relative rates of the competitive reactions in the combined iodination scheme has been derived.</p>			
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